Annals of Oncology **10**: 677–683, 1999.

Original article

Long-term evolution of renal function in patients with ovarian cancer after whole abdominal irradiation with or without preceding cisplatin*

D. P. Schneider,[1] H.-P. Marti,[2] C. Von Briel,[1] F. J. Frey[2] & R. H. Greiner[1]

[1]*Department of Radiation Oncology,* [2]*Division of Nephrology, University of Bern, Inselspital, Bern, Switzerland*

Summary

Background: The upper limit of the natural decline in creatinine clearance is 1 ml/min/year. To define the loss of renal function, we started a long-term assessment of patients with ovarian cancer treated by whole abdominal irradiation (WAI) with preceding cisplatin chemotherapy (CDDP) and second-look laparotomy (SLL).

Patients and methods: We analyzed the creatinine clearance over time of 56 patients treated from 1982 to 1988 for ovarian cancer. Thirty-one of 56 patients had received WAI after their initial surgery, and 25 of 56 patients had undergone CDDP therapy followed by SLL, and then WAI after their initial surgery. Median follow-up was 99 months (7–156). Twenty of 56 patients accepted our invitation for additional assessment of tubular function, nine of the 31 patients without CDDP therapy and SLL, and 11 of the 25 patients with CDDP followed by SLL and WAI.

Ten of twenty patients had received four to six cycles CDDP, 80 mg/m^2/cycle, and one patient nine cycles. The median total dose for each kidney was 1450 cGy (480–1690).

Results: The mean creatinine clearance decreased from 84 ml/min to 66 ml/min. Seventy-six percent of the 25 patients who had undergone CDDP therapy, SLL and WAI had declines of more than 1 ml/min/year, 64% of these patients of more than 2 ml/min/year. For the 31 patients who had received WAI after their initial surgery, the corresponding numbers were 71% and 55%, respectively. The tubular function of the 20 patients who had undergone the additional investigations was not impaired.

Conclusion: The decline in renal function after WAI is more pronounced than in healthy subjects. The treatment with cisplatin and SLL prior to WAI does not seem to contribute to this loss of kidney function.

Key words: cisplatin (CDDP), nephrotoxicity, ovarian cancer, whole abdominal irradiation (WAI)

Introduction

Adverse effects of irradiation on kidneys were first discussed by Baerman et al. in 1904 [1]. In 1952 and 1964, Kunkler and Luxton described clinical syndromes of radiation nephropathy by the analysis of patients treated for seminoma [2, 3]. Many patient reports of renal disorders after irradiation subsequently followed in rapid sequence [4–18]. Hallmarks of chronic radiation nephropathy are arterial hypertension, glomerular sclerosis/hyalinization, fibrinoid changes in arterioles and interlobular arteries, tubular atrophy and interstitial fibrosis [19].

A task force under the direction of the National Cancer Institute defined tolerance doses of various organs and tissues to therapeutic irradiation and published their recommendations in 1991 [20]. To support these recommendations, further systematic clinical studies are warranted. Cassady stressed in a recent article the need for well designed studies with long follow-up periods to accurately assess late radiation toxicity [21].

In this context, we examined the radiation nephropathy of our patients with advanced and non-advanced ovarian cancer who were treated in controlled protocols by surgery followed by either CDDP, second-look laparotomy and WAI or WAI exclusively following surgery. The long-term assessment examined especially the impact and mutual influence of the two potentially nephrotoxic agents, CDDP and irradiation, sequentially given, on renal function.

Patients and methods

From 1982 to 1988, a total of 136 patients, aged 14 to 82 years, all with epithelial ovarian cancer, were treated by surgery followed by either cisplatin (CDDP), second-look laparotomy and WAI, or by WAI alone. Of these 136, nine foreign patients were lost to follow-up, and 71 died sometime after therapy. 67 of causes related to the ovarian cancer; none, however, suffered from kidney failure.

Study group

The remaining 56 patients comprised our study group. The median follow-up period was 99 months (7–156). Twenty of 56 patients agreed

* The first and second author contributed equally to the present investigation.

Table 1 Characteristics of the 20 investigated patients.

Patient number	Age at study begin	Observation period (years)	CDDP (mg)	Radiation technique for WAI	Single kidney doses (Gy)	Total kidney doses (Gy)	CCl at study begin/end (ml/min)	Diabetes mellitus or hypertension
1	49	7	4 × 140	OF	0.65	10.20	81/67	–
2	60	9	5 × 130	OF	0.65	12 80	83/29	H°
3	57	6	4 × 140	OF	0 65	16.20	84[a]/67	–
4	42	12	5 × 120	MS	1 15	14.50	85/84	–
5	46	10	4 × 150	OF	0.65	15.00	112/51	DM
6	57	10	5 × 130	OF	0.65	11.80	83/46	H
7	53	9	4 × 140	OF	0.65	15.00	87[a]/49	–
8	30	13	9 × 85	MS	1.15	14.50	92/78	–
9	65	10	6 × 120	OF	0.65	15.00	64/59	H
10	49	8	5 × 140	OF	0.65	4.80	95[a]/74	H
11	44	5	4 × 140	OF	0.65	16.90	79/78	H
12	51	9	–	OF	0.65	15.00	93[a]/64	–
13	33	11	–	MS	1.15	14.50	100[a]/67	–
14	53	12	–	MS	1.15	14.50	81[a]/52	–
15	60	11	–	MS	1.15	14.50	68[a]/37	H
16	53	12	–	OF	0.65	11.00	77[a]/49	–
17	37	10	–	MS	1.15	14.50	78[a]/71	–
18	45	6	–	OF	0.65	15 00	116[a]/52	–
19	65	12	–	MS	1.15	14.50	74[a]/43	–
20	62	9	–	OF	0.65	15 00	81[a]/49	DM

Abbreviations: CDDP – cis-diammmedichloride platinum; WAI – whole abdominal irradiation; CCl – creatinine clearence, values followed by [a] were calculated according to Cockcroft et al. [22] or Jeliffe et al. [23]; OF – open field; MS – moving strip; DM – diabetes mellitus, H – hypertension (H° = in addition to hypertension, history of excessive consumption of phenacetin).

to undergo investigaton of renal-tubular function in addition to assessment of glomerular filtration rate. These 20 patients constituted the investigated group, while the remaining 36 patients formed the non-investigated group.

In the investigated group, 11 of 20 patients (FIGO stage: 2 × IC, 1 × IIB, 2 × IIC, 6 × III) had received CDDP chemotherapy, 10 patients four to six cycles with 80/m^2/cycle and 1 patient nine cycles. In addition to CDDP as the only nephrotoxic agent, combination chemotherapy contained either melphalan, melphalan and hexamethylmelamin, or cyclophosphamide. The FIGO stage of the nine investigated patients without CDDP chemotherapy were 5 × IB/C, 2 × IIB, and 2 × III. In the non-investigated group 14 of 36 patients received CDDP chemotherapy (FIGO stage: 3 × IC, 5 × 2B/C, and 6 × III). The FIGO stage of the 22 patients in the non-investigated group who did not receive CDDP chemotherapy were 21 × IB/C, and 1 × III.

For the investigation of a possible adverse effect of cisplatin on renal function, we pooled patient data from the investigated (n = 20) and non-investigated (n = 36) patients and classified these individuals into two new groups, WAI patients treated with cisplatin (n = 25) and those receiving no cisplatin chemotherapy (n = 31). Median age and follow-up periods for the former group were 52 years (28–72) and 83 months (26–156), respectively, and for the latter group 53 years (33–82) and 102 months (7–148), respectively.

Kidney irradiation dose

To deliver whole abdominal irradiation (WAI), the *moving strip* and, later, the *open field* techniques were used. Patients were treated in prone position using anterior–posterior fields for a target volume extending from the domes of the diaphragms to the lower border of the obturator foramina; 5 H.V.L. lead shielding were inserted to shield the kidneys from the posterior field. Kidney shielding was localised by an intravenous pyelogram at the time of treatment simulation. Cobalt-60 beam was employed for the moving strip technique. The single dose was 230 cGy adapted to an isodose, which encompassed the whole abdomen rather homogeneously. For the open field technique the energies of 8 or 16 MeV from the linear accelerator were used. The single dose of 130 cGy was calculated for mid-plane. The median total kidney dose for both techniques was 14.5 Gy (4.8–16.9 Gy) with single kidney doses in the range of 1 15 Gy (moving strip) and of 0.65 Gy (open field). Terminations of treatment, principally because of hematotoxicity, are the reason for the broad range of the kidney doses.

Study group: Investigated patients (n = 20)

The median age of the investigated group at diagnosis was 52 years (30–65). All 20 patients were tumor-free at the time of the study. The median follow-up period of these patients was 117 months (61–156). Additional clinical data and details of radiation and chemotherapy are given in Table 1. Analyses of all 20 patients included clinical history, physical examination, blood and urine tests and kidney ultrasound. At the end of the observation period, 24-hour urine specimens were collected from all patients in order to determine *creatinine clearance*, *proteinuria*, and *tubular function* by excretion of uric acid, phosphate and glucose. Urine analysis including measurement of pH for assessment of tubular acidification was performed in random morning urine samples. Prior to any therapy such as WAI or chemotherapy, creatinine clearance was measured from 24-hour urine specimens in eight patients. For the remaining 12 patients, the creatinine clearance was calculated using the formulas reported by Cockcroft et al. [22] and Jelliffe et al. [23]. To predict creatinine clearance, the former relies on serum creatinine, body weight and age, and the latter on serum creatinine and age only. In our analyses, we used the first formula, except in a few patients with significant obesity (body mass index >30 kg/m^2), in whom we applied the second formula because of overestimation of creatinine clearance by inclusion of excessive body weight into the calculations.

Study group: Non-investigated patients (n = 36)

The median age of the non-investigated group at diagnosis was 57 years (28–72). Twenty-three of the 36 patients were tumor-free at the time of the renal function investigations. The median follow-up period

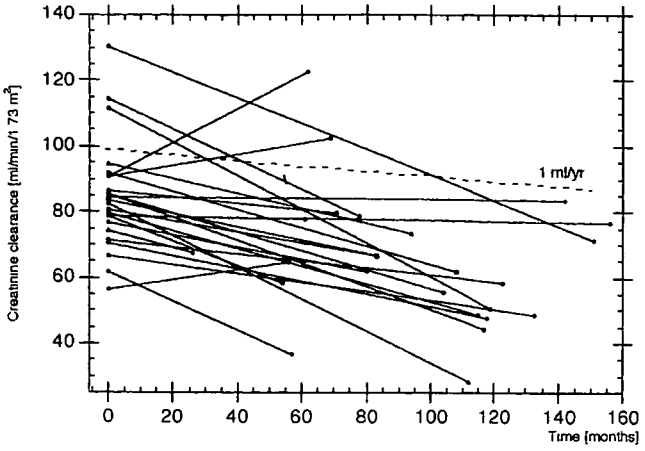

Figure 1 Creatinine clearance as a function of time in 25 patients treated with CDDP and WAI. The dashed line indicates the natural age-related decline of the creatinine clearance (1 ml/year) according to Bjornsson [24]. A total of 76% of the patients had a decline greater than 1 ml/year, and 64% of more than 2 ml/year.

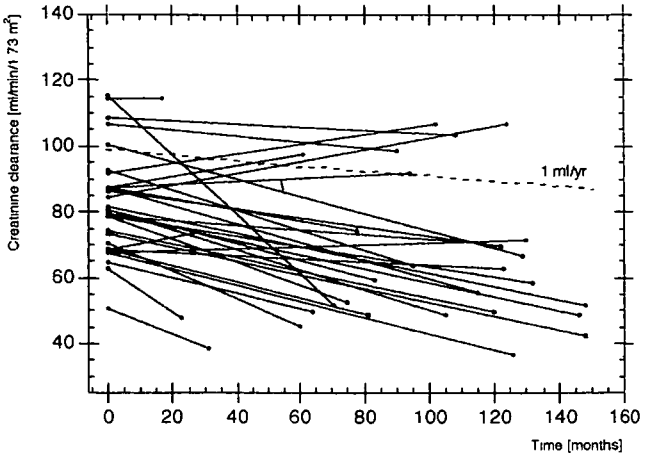

Figure 2. Creatinine clearance as a function of time in 31 patients treated with WAI only. The dashed line represents the natural decrease of the creatinine clearance with age (1 ml/year), according to Bjornsson [24]. A total of 71% of the patients demonstrated a decline greater than 1 ml/year, and 55% of more than 2 ml/year.

of these patients was 81 months (7–158) Creatinine clearance values were calculated in all of these patients, as stated above.

Kidney function

Kidney function in all 56 patients of both the *investigated* and the *non-investigated* groups was analyzed as a function of time. In addition, the evolution of the glomerular filtration rate in these patients was compared to the age-related, natural decline in creatinine clearance [22–27] Importantly, according to Bjornsson et al [24], creatinine clearance in adults, such as our study patients, decreases by approximately 1 ml/min/year independent of gender. This value was used as reference for the analyses of our patients.

Results

General evolution of glomerular filtration rate

The main purpose of this study was to investigate the glomerular filtration rate as a function of time after WAI. In our 56 patients the decline in creatinine clearance was more pronounced than in healthy subjects during an identical observation period. The mean creatinine clearance in our patients decreased by 18 ml/min (from 84 ± 16 to 66 ± 21 ml/min; $P < 0.05$) during the median and mean observation period of eight years.

Effect of CDDP and WAI versus *WAI alone on glomerular filtration rate*

During the study period, the decline in mean creatinine clearance of patients exposed to CDDP and irradiation ($n = 25$) was 19 ml/min, very close to the 16 ml/min in patients treated by radiotherapy alone ($n = 31$), when a comparable observation time was considered. Additionally, the results of the creatinine clearances of these two patient groups were plotted against time (Figures 1 and 2). As shown in Figure 1, 19 of 25 (76%) of the patients in the group treated with chemotherapy and irradiation had declines in creatinine clearance greater than 1 ml/year (with 1 ml/year as the natural decline in renal function of a normal adult population of comparable age; 24). Moreover, 16 of 25 (64%) of these patients had losses of more than 2 ml/year. In the group with irradiation alone, the numbers were 71% and 55%, respectively (Figure 2).

Effect of CDDP and WAI on kidney function of the investigated patient group

Kidney function in the 20 patients in the investigated group was analyzed in greater detail with respect to glomerular filtration rate, kidney size, and renal tubular function. Relevant data of patients, treatment methods and laboratory results are summarized in Tables 1 and 2.

Glomerular filtration rate. Altogether, during the follow-up period of 117 months (61–156), the mean creatinine clearance significantly decreased from 86 ± 13 ml/min to 58 ± 15 ml/min ($P < 0.05$), with a mean value for the patients with CDDP and WAI of 62±16 ml/min and for the patients with WAI alone 54 ± 11 ml/min. At the end of the observation period, 11 of the 20 patients demonstrated creatinine clearances below 60 ml/min; in 9 of these 11 patients, creatinine clearance was 40–59 ml/min, and in the remaining two, 39 and 29 ml/min.

In these 20 patients, we were not able to correlate renal radiation dose and decline in kidney function on the basis of the data reported in Table 1.

Tubular function. Renal tubular function of the 20 investigated-group patients was analyzed in detail. The results are summarized in Table 2.

Tubular reabsorption of phosphate (TRP) measured in individuals with normal renal function (creatinine clearance) was previously reported by Popovtzer et al. to be

Table 2. Renal tubular function of the 20 investigated patients.

Patients	Potassium (3.5–4.7 mmol/l)	Magnesium (0.70–0.95 mmol/l)	Glucosuria (< 2.80 mmol/ 24 hours)	Proteinuria (< 0.15 g/ 24 hours)	FE_{UR} (6%–12%)	TRP % (85%)	pH in spot urine
Group of patients treated with CDDP and WAI							
1	3.9	0.78	0	< 0.15	7.6	86	5
2	3.6	0.62	0	0.25	13 6	70	5
3	4.6	1.06	0	< 0.15	13.5	84	5
4	4.3	0.82	0	< 0.15	13.1	77	5
5	4.3	0.68	1049	< 0.15	18.3	73	5
6	4.4	0.78	0	< 0.15	9.2	78	5
7	4.8	0.92	0	< 0.15	6.4	66	5.5
8	3.7	0.75	0	< 0.15	19	76	5
9	3	0.7	0	< 0.15	16.3	73	5
10	4	0.74	0	< 0 15	11.4	87	5
11	3.8	0.75	0	< 0 15	8.7	76	6.5
Mean (1–11)[a]	4.0 ± 0.5	0.78 ± 0.12			12.5 ± 4.1	77 ± 6	
Group of patients treated with WAI only							
12	4 4	0.78	0	< 0.15	11.5	68	5
13	3.6	0.75	0	< 0.15	10.6	63	5
14	4 2	0.83	0	< 0.15	10 1	71	5
15	5.3	0.76	0	< 0.15	9	63	5
16	4.2	0.74	0	< 0.15	11 4	78	5
17	3.8	0.54	0	< 0.15	13.3	–	5
18	4	0.81	0	< 0.15	8.8	79	5
19	4.5	0.94	0	< 0.15	14.4	79	5
20	4	0.75	185	< 0.15	20.7	76	5
Mean (12–20)	4.2 ± 0.5	0.77 ± 0.11			12.2 ± 3.5	72 ± 6	

All biochemical results were obtained at the end of the observation period.

[a] Patients 1–11 received WAI and additional chemotherapy as depicted in Table 1

FE_{ur} (%): Fractional excretion of uric acid = $\frac{\text{Uric acid clearance}}{\text{creatinine clearance}} \times 100$.

TRP: Tubular reabsorption of phosphate = 1 − fractional excretion of phosphate.

in the order of 85% [28]. In our 20 patients, TRP was 77% ± 6% in the 11 cases treated with CDDP and WAI and 72% ± 6% in the 9 individuals treated with radiotherapy alone. Considering reduced mean creatinine clearances of 62 ± 16 ml/min in the former and of 54 ± 11 ml/min in the latter group, the small reduction in TRP due to the increase in fractional excretion of phosphate is an expected finding according to Popovtzer et al. [28]. Thus, the small reduction in TRP due to increased fractional phosphate excretion merely reflects the reduction in renal function and may in addition be interpreted as a consequence of mild secondary hyperparathyroidism.

The *fractional excretion of uric acid* (FE_{ur}) was 12.5% ± 4.1% in patients treated with CDDP and 12.2% ± 3.5% in patients not exposed to chemotherapy. These results are not significantly different from the normal excretion of uric acid, which is generally on the order of 6% to 12% of the filtered load [29] and 12.0% ± 2.9% in non-pregnant women [30]. However, as renal function deteriorates, there is a progressive increase in excretion and a relative clearance of uric acid because of increased tubular secretion of urate and incomplete reabsorption of filtered urate [31]. According to a plot of glomerular filtration rate *versus* FE_{ur} by Calabrese et al. [32], both mean values of FE_{ur} obtained in our patient subgroups are only slightly above the expected value of about 11%; however, in that publication 10% was considered to be the upper limit of a normal FE_{ur} in unimpaired kidney function.

Except in the two patients with known diabetes mellitus, no *glucosuria* due to tubular damage was found. Only one patient showed a slight *proteinuria* of 0.25 g/day, which may well be explained by hypertension and past abuse of phenacetin. In 18 of the 20 patients, a pH of 5.0 was measured in random urine samples. Although this finding does not entirely exclude an acidification defect [33], a significant distal renal tubular disorder with respect to acid excretion seems unlikely.

Finally, *potassium* and *magnesium* measured in serum were in the normal range except in one patient with a potassium of only 3.0 mmol/l (3.5–4.7 mmol/l) and in three patients with borderline to mild hypomagnesemia of 0.54–0.68 mmol/l (0.70–0.95 mmol/l). These findings satisfactorily excluded tubulopathy with loss of electrolytes, typically found in cisplatin- induced nephropathy.

Kidney size. The kidney length found in normal adult females is slightly less than 11 cm [34]. However, renal length decreases by 2 cm between the ages of 50 and 80 years [35]. Therefore, as measured by ultrasound in the investigated group, renal size was practically not affected, with a mean of 10.0 ± 1.1 cm in the CDDP-treated group and of 10.3 ± 1.1 cm in the group with radiotherapy alone. Most likely, the only minimal reduction of kidney size reflected the glomerular function slightly reduced

Table 3. Patient reports of radiation nephropathy.

Author, year [Ref.]	Patient number	Underlying disease	Total kidney dose (Gy)	Chemotherapy	Follow-up (years)	Kidney function (GFR)
Luxton, 1964 [3]	2.54	Mostly seminoma	25–30	Not reported	⩽14	ARN: 20, and CRN: 22 patients
Thompson, 1971 [17]	2.67	Gastric hypersecretion	15–20 to left kidney	Not given	8–19	RN: 31 patients (9 deaths)
Arneil, 1974 [4]	2.2	Nephro-blastoma	15/20 to not nephrectomized kidney	Actinomycin D and vincristine	2	ARN: 2 patients
Keane, 1976 [12]	2.2	Ovarian carcinoma	25 and 27 to both kidneys	Not given	10 and 11 months	ESRD and CCl of 30ml/min
Churchill, 1978 [6]	2.1	Testicular carcinoma	38 to both kineys	Bleomycin and vinblastine	9 months	ARN (CCl: 67 ml/min)
Le Bourgeois, 1979 [15]	1.74	Lymphoma	15–45 to left kidney	Not reported	3–5	Stable renal function
Birkhead, 1979 [5]	2.17	Hodgkin lymphoma	40 to left kidney	Only for 1 patient reported	3–6	Stable renal function
Kim, 1984 [13]	1 18	NHL	22–45 to one kidney	Not reported	2–8	RN: 9 patients (CCl 5216 ml)
Willet, 1986 [18]	2.86	Abdominal carcinoma, lymphoma and sarcoma	26–61 to one kidney	Not reported	3 (1–9)	Mean decrease of CCl = 17/min
Markoe, 1989 [44]	2.12	Ovarian cancer, lymphoma, testicular tumor	17–25 to both kidneys	Not reported	0.5–14	CRN: 1 patient (CCl· 48 ml/min)
Dewitt, 1990 [7]	2.26	NHL, Hodgkin lymphoma, ovarian cancer, seminoma	17–40 (uni- and bilateral)	Not reported	3–5	5 patients with 25% decline of CCl
Flentje, 1993 [9]	2.142	Seminoma	19–28 to both kidneys	Not reported	8 (2–21)	'Clinical manifest' CRN: 7 patients
Irwin, 1996 [36]	1.60	Ovarian cancer, NHL, carcinoid	19 (7–23) to both kidneys	Not given	9 (5–20)	Stable renal function
Schneider [present study]	56	Ovarian cancer	14.5 (5–17) to both kidneys by WAI	Cisplatin to 25/56 pat. prior WAI	8 (0.5–13)	Decrease in mean CCL from 84 to 66 ml/min

Abbreviations: ARN – acute radiation nephritis, CRN – chronic radiation nephritis; NHL – non-Hodgkin's lymphoma; CCL – creatinine clearance; ESRD – end-stage renal disease.

over many years and present at the observation time. Even in the two patients with the lowest creatinine clearances of 29 ml/min and 37 ml/min, kidney length was still close to 9 cm. These findings confute pre-existing chronic renal failure. In addition, renal ultrasound examination revealed no further pathological findings such as increased echogenicity, cortical atrophy or parenchymal cysts in any of the 20 patients.

Comorbidity. Co-morbid conditions were found in eight of the patients in this group which could potentially have an adverse effect on kidney function, as shown in Table 2. Arterial hypertension was treated in six patients, including the one with excessive consumption of phenacetin, for durations of five months to six years. However, the mean creatinine clearances of hypertensive and normotensive patients were almost identical: 54 ml/min and 60 ml/min, respectively. Two patients suffered from diabetes mellitus. Only one patient with hypertension, who also had the worst renal function of the 20 patients analyzed, showed borderline proteinuria of 0.25 g/24 h (patient 2, Table 1). In addition, this patient was the only one who demonstrated significant abnormality in urinalysis, namely microhematuria.

Discussion

Radiation nephritis is a well-known entity which is, however, difficult to analyze quantitatively because of many confounding variables. The key findings of 13 previously published studies or case reports are summarized in Table 3. The observed effects of irradiation on renal function are heterogeneous, depending on total renal dose, irradiated renal volume, on uni- or bilateral kidney irradiation, and on length of patient follow-up periods. The duration of the present study is extensive and the patient numbers high, comparable to only four other studies (Table 3) [3, 9, 17, 36].

Chemotherapy is a common variable in the assessment of radiation nephritis, and chronic renal failure is a rare but well-described complication of cisplatin [37–39]. Remarkably, there is no published report separately analyzing the effects of chemotherapy on the course of radiation nephropathy, so our study is thus unique with respect to its direct comparison of irradiated patients treated with and without cisplatin. However, we found no differences with respect to cisplatin. Experimental studies analyzing mice or rats clearly demonstrated an enhancing effect of cisplatin on kidney damage caused by irradiation [40–43]. In addition, second-look laparotomy had no negative effect on renal function in the patients who received chemotherapy.

Other important confounding factors are hypertension and diabetes mellitus. As in most other studies, the precise adverse effects of these two underlying diseases on kidney function in our subjects is difficult to judge, since the durations and treatments of hypertension and diabetes mellitus are not known. In addition, high blood pressure in our patients may be a result of radiation nephropathy but could also represent essential hypertension, especially in the presence of well-preserved kidney function, such as in the study patients 10 and 11 (Table 1). However, there were no cases of malignant hypertension and in our *investigated-patient group* kidney function did not differ in hypertensive and normotensive individuals.

The decline of renal function in our population was pronounced despite the low single doses of 0.65 and 1.15 Gy. The decrease of the mean glomerular filtration rate in our 56 patients was more than twice the expected natural age-related decline of 1 ml/min/year [24].

In addition to creatinine clearance, we analyzed several factors reflecting renal tubular functions. Despite the reduction of glomerular filtration rate, renal tubular function was well preserved. Therefore, most of the late-effect damage of low-dose irradiation to the kidney may have occurred to endothelial cells present in arterioles and in glomerular capillaries rather than to tubular cells due to interstitial inflammation [13].

In summary, we found no patients with chronic radiation nephropathy in our series of 56 patients who received WAI or CDDP and SLL followed by WAI after epithelial ovarian cancer surgery. Nevertheless, analyses of kidney function over time showed a more pronounced decline of creatinine clearance in our patients than in the normal population. Interestingly, the addition of cisplatin and SLL did not adversely influence the decrease in renal function.

Acknowledgements

We particularly thank M. Giudici, MD, Institute of Diagnostic Radiology, Inselspital, for the ultrasound examinations in our patients.

References

1. Baerman G, Linser P. Ueber die lokale und allgemeine Wirkung der Röntgenstrahlen. München Med Wochenschr 1904; 7: 996.
2. Kunkler PB, Farr RF, Luxton RW. The limit of renal tolerance to X-rays. Br J Radiol 1952; 25: 190–201.
3. Luxton RW, Kunkler PB. Radiation nephritis. Acta Radiolog Ther Phys Biol 1964, 2: 169–78.
4. Arneil GC, Emmanuel IC, Flatman GE et al Nephritis in two children after irradiation and chemotherapy for nephroblastoma. Lancet 1974; 18· 960–3
5. Birkhead BM, Dobbs CE, Beard MF et al. Assessment of renal function following irradiation of the intact spleen for Hodgkin's disease. Radiology 1979; 130: 473–5.
6. Churchill DN, Hong K, Gault MH. Radiation nephritis following combined abdominal radiation and chemotherapy (bleomycin–vinblastine). Cancer 1978; 41: 2162–4
7. Dewitt L, Anninga JK, Hoefnagel CA et al. Radiation injury in the human kidney: A prospective analysis using specific scintigraphic and biochemical endpoints. Int J Radiat Oncol Biol Phys 1990; 19: 977–83.
8. Fajardo LF, Brown JM, Glatstein E. Glomerular and juxtaglomerular lesions in radiation nephropathy. Radiat Res 1976; 68: 177–83.
9. Flentje M, Hensley F, Gademann G et al. Renal tolerance to non homogeneous irradiation: Comparison of observed effects to predictions of normal tissue complication probability from different biophysical models. Int J Radiat Oncol Biol Phys 1993; 27: 25–30.
10. Greenberger JS, Weichselbaum RR, Cassady JR. Radiation nephropathy In Rieselbach RE, Garnick MB (eds): Cancer and Kidney. Philadelphia, PA: Lea & Febiger 1982. 814–23.
11. Jordan SW, Anderson RE, Lane RG et al. Fraction size, dose and time dependence of X-ray induced late renal injury Int J Radiat Oncol Biol Phys 1985; 11: 1096–101.
12. Keane WF, Crosson JT, Staley NA et al. Radiation-induced renal disease. Am J Med 1976; 60: 127–37.
13. Kim TH, Sommerville PJ, Freeman CR. Unilateral radiation nephropathy. The long-term significance. Int J Radiat Oncol, Biol Phys 1984; 10: 2053 9.
14. Lebesque JV, Stewart FA, Hart AAM. Analysis of the rate of expression of radiation-induced renal damage and the effects of hyperfractionation. Radiother Oncol 1986; 5: 147–57.
15. Le Bourgeois JP, Meignan M, Parmentier C et al. Renal consequences of irradiation of the spleen in lymphoma patients. Br J Radiol 1979; 52: 56–60.
16. Madrazo AA, Churg J. Radiation nephritis chronic changes following moderate doses of radiation. Laborat Invest 1976; 34: 283–90.
17. Thompson PL, Mackay IR, Robson GSW et al. Late radiation nephritis after gastric X-irradiation for peptic ulcer. Q J Med 1971; 157 (new series, XL): 145 -57.
18. Willet CG, Tepper JE, Orlow EL et al. Renal complications secondary to radiation treatment of upper abdominal malignancies. Int J Radiat Oncol Biol Phys 1986; 12: 1601–4.

19. Heptinstall RH. Irradiation inury and effects of heavy metals. In Heptinstall RH (ed): Pathology of the Kidney (4th edition). Boston/Toronto/London: Little, Brown and Company 1992: 2085–95.
20. Emami B, Lyman J, Brown A et al. Tolerance of normal tissue to therapeutic irradiation Int J Radiat Oncol Biol Phys 1991; 21: 109–22.
21. Cassady JR. Clinical radiation nephropathy. Int J Radiat Oncol Biol Phys 1995; 31: 1249–56.
22. Cockcroft DW, Gault MH. Prediction of creatinine clearance from serum creatinine. Nephron 1976; 16: 31–41.
23. Jelliffe RW. Creatinine clearance. Bedside estimate. Ann Intern Med 1973; 79: 604–5.
24. Bjornsson TD. Use of serum creatinine concentrations to determine renal function. Clin Pharmacokinet 1979; 4: 200–2.
25. Kampman J, Siersbaek-Nielsen K, Kristensen M et al. Rapid evaluation of creatinine clearance. Acta Med Scand 1974; 196: 517–20.
26. Rowe JW, Andres R, Tobin JD et al. Age-adjusted standards for creatinine clearance. Ann Intern Med 1976; 84: 567–9.
27. Rowe JW, Andres R, Tobin JD et al. The effect of age on creatinine clearance in man. A cross-sectional and longitudinal study. J Gerontol 1976; 31: 155–63.
28. Popovtzer MM, Schainuck LI, Massry SG et al. Divalent ion excretion in chronic kidney disease: Relation to degree of renal insufficiency. Clin Sci 1970; 38: 297–307.
29. Rose BD. Clinical Physiology of Acid-Base and Electrolyte Disorders. 4th edition. New York: McGraw-Hill 1994; 91.
30. Dunlop W, Davidson JM. The effect of normal pregnancy upon the renal handling of uric acid. Br J Obs Gynecol 1977; 84: 13–21.
31. Danovitch GM, Weinberger J, Berlyne GM. Uric acid in advanced renal failure. Clin Sci 1972, 43: 331–41
32. Calabrese G, Simmonds HA, Cameron JS et al. Precocious familial gout with reduced fractional urate clearance and normal purine enzymes. Q J Med 1990; 75: 441–50.
33. Halperin ML, Richardson RMA, Bear RA et al. Urine ammonium: The key to the diagnosis of distal renal tubular acidosis. Nephron 1988; 50: 1–4.
34. Venkatachalam MA, Kriz W. Anatomy. In Heptinstall RH (ed): Pathology of the Kidney, 4th edition. Boston/Toronto/London: Little, Brown and Company 1992; 1–93.
35. McLachlan M. Anatomic structural and vascular changes in the aging kidney. In Macias-Nunez JF, Cameron JS (eds): Renal Function and Disease in the Elderly. London: Buttersworths 1987; 67–93.
36. Irwin C, Fyles A, Wong CS et al. Late renal function following whole abdominal irradiation. Radiother Oncol 1996; 38: 257–61.
37. Brillet G, Deray G, Lucsko M et al. Definitive end-stage chronic kidney failure after cisplatin treatment. Nephrol 1993; 14 (5). 227–9.
38. Dentino M, Luft FC, Yum MN et al. Long term effect of cis-diamminedichloride platinum (CDDP) on renal function and structure in man. Cancer 1978, 41 (4): 1274–81
39. Jakob S, Arnold W, Marti HP. Progressive renal failure after cisplatin therapy. Nephrol Dial Transplant 1996; 11: 370–3.
40. Moulder JE, Fish BL. Effect of sequencing on combined toxicity of renal irradiation and cisplatin. Natl Cancer Inst Monogr 1988, 6. 35–9.
41. Stewart FA, Bohlken S, Begg AC et al. Renal damage in mice after treatment with cisplatin alone or in combination with X-irradiation. Int J Radiat Oncol Biol Phys 1986; 12 (6): 927–33.
42 Stewart FA, Luts A, Begg AC. Tolerance of previously irradiated mouse kidneys to cis-diaminedichloroplatinum. Cancer Res 1987; 47. 1016–21.
43. Stewart FA, Williams MV. The urinary tract. In Scherer E, Streffer C, Trott K (eds): Radiopathology of Organs and Tissues Berlin/Heidelberg/New-York: Springer-Verlag 1991; 405–52.
44. Markoe AM, Brady LW, Swartz C et al. Radiation effects on renal function. In Vaeth M, Meyer JL (eds): Radiation Tolerance of Normal Tissues. Basel: Karger, Front Radiat Ther Oncol 1989; 23: 310–22.

Received 25 November 1998; accepted 9 March 1999.

Correspondence to:
R. H. Greiner, MD
Department of Radiation Oncology
Inselspital Bern
CH-3010 Bern
Switzerland